Measurement of the excretion of catecholamines appears to provide an indirect but objective measure of pain which may be useful in the assessment of analgesic drugs. There is a large individual variation and the method is likely to be useful only in crossover trials when the patient provides his own control. The differences in treated and untreated patients are not large and urine collections for at least three days are likely to be required to detect them. In a previous experiment, there were no significant differences in treated and untreated patients with urine collected for three 12 h periods overnight. In this study, a variety of treatments was used and in all cases there was a good response to treatment. Less marked pain relief might be undetectable or require longer periods of collection.

The findings of this study could also be explained by a direct action of analgesic and anti-inflammatory drugs on some aspect of catecholamine metabolism, which must be considered when the method is applied to individual compounds.

It is perhaps surprising that changes in noradrenaline were comparable to those of adrenaline, but stress appears to increase the excretion of both catecholamines (Levi, 1968). Because noradrenaline is excreted in much larger amounts, it is likely to provide the more useful measurement of pain.

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PROPRANOLOL ON TESTS OF VISUAL FUNCTION AND CENTRAL NERVOUS ACTIVITY

Propranolol has been shown to have therapeutic value in the treatment of some patients with anxiety states (Granville-Grossman & Turner, 1966), but its mechanism of action is uncertain. β-blockade appears to be the principal action, as the +-isomer of propranolol, which has relatively little β-blocking activity, is ineffective in anxiety (Bonn & Turner, 1971). Practolol penetrates the brain to only a small extent but appears to be effective in treatment of anxiety (Bonn, Turner & Hicks, 1972), which suggests a peripheral, rather than central, mode of action. We have examined the effect of propranolol in therapeutic doses in normal subjects to determine if evidence of a central nervous effect could be detected on reaction time and on a test of hand-eye co-ordination which has previously been shown to be sensitive to the effect of some centrally acting drugs including promethazine (Molson, Mackay, Smart & Turner, 1966) and lorazepam (Bell, Dickie, Stewart-Jones & Turner, 1973). In any study of centrally acting drugs in man involving a response to a visual stimulus, the possibility of a drug effect on the peripheral visual apparatus must be considered, and therefore, in addition to these tests of central nervous function, tests of visual activity were also performed.

Six healthy volunteers aged 20-25 years with normal colour vision and visual acuities of 6/4.5 or better in both eyes, and in good health, who were receiving no other medication, were given racemic propranolol, 40 or 80 mg, or a placebo in tablet form in random order based on two latin-square designs, under double-blind conditions, each treatment being separated by at least one week. The tests were carried out at the same time in the afternoon after a standard light lunch. Subjects avoided coffee, tea, alcohol and nicotine on the test days. Tests were made before and at 1.5 and 3 h after treatment. The subjects had been familiarized with the procedures before the investigation. In the hand-eye co-ordination test they had reached a plateau of performance to minimize further learning effects.

The tests were of (a) refraction, (b) visual acuity, (c) amplitude of accommodation, (d) oculomotor balance, (e) visual fields and (f) hand-eye co-ordination, made according to Molson *et al.* (1966) and Austen, Gilmartin & Turner (1971). In addition reaction time was measured

Table 1 Mean pulse rate (beats/min), reaction time (s) and hand-eye co-ordination scores (arbitrary units) before and at 1.5 and 3 h after propranolol 40 mg or 80 mg, or placebo in six subjects, together with the standard error of differences between the means (S.E.M.).

		Placebo		*Propranolol (40 mg)*		*Propranolol (80 mg)*		
		Before	*After*	*Before*	*After*	*Before*	*After*	*s.e. mean*
Pulse rate (beats/min)	1.5 h	76.83	71.00	76.00	63.83	72.67	57.83	2.416
	3 h	76.83	69.83	76.00	60.5	72.67	57.17	1.650
Reaction time (s)	1.5 h	0.268	0.270	0.268	0.275	0.263	0.282	0.0061
	3 h	0.268	0.264	0.268	0.270	0.263	0.295	0.0098
Hand-eye co-ordination (arbitrary score)	1.5 h	124.53	124.28	124.94	124.39	124.78	124.44	0.866
	3 h	124.53	126.97	124.94	124.00	124.78	124.28	1.458

using a 'Decade' counter which was started by the same switch button which initiated the stimulus. This was a green light, which retro-illuminated an opal disc 1.2 mm in diameter, set in a wooden screen 60 mm long x 50 mm high. The subject registered his response by releasing a morse key, which stopped the counter.

The results obtained at 1.5 and 3 h after the two doses of propranolol were compared with those after placebo, all analyses being carried out on the data expressed as a change from the 0 h values.

No significant changes were found in refraction (spherical and cylindrical components), visual acuity, amplitude of accommodation (dioptres), oculomotor balance (relative exophoria in dioptres), and in visual fields.

Changes in pulse rate, reaction time and hand-eye co-ordination are shown in Table 1. There were significant differences in mean pulse rate between placebo and propranolol 40 mg ($P < 0.05$) and between placebo and propranolol 80 mg ($P < 0.01$) at 1.5 h and between placebo and both doses of propranolol at 3 h ($P < 0.01$). There were significant differences in mean reaction times between placebo and propranolol 80 mg at 1.5 h ($P < 0.05$) and at 3 h ($P < 0.01$). There were no significant differences between treatments for hand-eye co-ordination at 1.5 h but at 3 h there was a significant difference between placebo and propranolol 40 mg ($P < 0.05$).

The dose response reduction in heart rate produced by propranolol suggests a satisfactory absorption and pharmacological effect of the drug in these experimental subjects.

The prolongation of reaction time after propranolol 80 mg and the impairment of hand-eye co-ordination which was most marked after 40 mg although also seen with the 80 mg dose, is consistent with a central depressant action of the drug, particularly as no changes were found in the peripheral components of visual function. Furthermore, the maximum changes in all three tests were found in the 3 h measurements, which again suggests a true pharmacological effect.

Previous studies of β-adrenoceptor blocking drugs on central nervous function have produced conflicting results. Lader & Tyrer (1972) found no unequivocal evidence of central effects with propranolol 120 mg or sotalol 240 mg in acute dosage in normal subjects, using tests of reaction time, key-tapping, card sorting, digit symbol substitution, symbol copying and E.E.G. recording. Turner & Hedges (1973) found no change in critical flicker frequency, serial subtraction or disc-dotting after oral (40 or 80 mg) and intravenous (0.1 or 0.2 mg/kg) oxprenolol. On the other hand, Glaister, Harrison & Allnutt (1973)

found a significant impairment of performance in a pursuit-rotor test after oxprenolol 0.2 mg/kg intravenously.

Although it would appear that any changes which occur in central nervous function after the usual oral doses (10-80 mg) of propranolol are small, it is possible that more marked changes might occur with the larger doses sometimes used in hypertension and angina pectoris. It is uncertain to what extent, if any, the small changes demonstrated in this study are important in mediating the therapeutic actions of propranolol in anxiety states.

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A SIMPLE SPECTROPHOTOFLUOROMETRIC METHOD FOR THE MEASUREMENT OF I.C.I. 66082 IN PLASMA AND URINE

Preliminary studies in animals with I.C.I. 66082, 4-(2-hydroxy-3-isopropylaminopropoxy) phenyl acetamide, indicated that it was a cardioselective β-adrenoreceptor blocking agent without intrinsic sympathomimetic or membrane activity (Barrett, Carter, Fitzgerald, Hull & Le Count, 1973; Harry, Knapp & Linden, 1973; Hainsworth, Karim & Stoker, 1973), and initial observations on its human pharmacology have shown that it is an effective β-adrenoceptor blocking drug in man (Graham, Littlejohns, Prichard, Scales & Southorn, 1973). The present work describes a simple spectrophotofluorometric method for the measurement of I.C.I. 66082 in plasma and urine, and gives the results obtained by this method for levels of the drug in plasma and urine of two normal male volunteers who received 200 mg of I.C.I. 66082 orally in a tablet formulation.

The excitation and emission spectra of I.C.I. 66082 are shown in Figure 1. With the emission wavelength set at 310 nm curve A was obtained by scanning the excitation spectrum of the pure drug in 0.5 M aqueous NaH_2PO_4 solution at a concentration of 5 μg/ml. On scanning the emission spectrum of the same sample with the excitation wavelength set at 280 nm, curve B was obtained. Three peaks occurred in the excitation spectrum, the main one being at 280 nm, and two peaks occurred in the emission spectrum, the main one being at 310 nm. In the present method for measuring I.C.I. 66082 the excitation wavelength was set at 280 nm and the emission wavelength at 310 nm.

The method used for plasma was as follows. To plasma (2 ml) was added 10 M NaOH (0.2 ml) and ethyl acetate (12 ml). The mixture was shaken